

Syndrome of the month

Treacher Collins syndrome

Michael J Dixon

Although the condition was probably first described by Thompson¹ in 1846, Treacher Collins syndrome is eponymously named after E Treacher Collins² who described the essential components of the condition in 1900. The first extensive review of the condition was detailed by Franceschetti and Klein³ in 1949, who used the term mandibulofacial dysostosis to describe the clinical features.

Clinical features

Treacher Collins syndrome is an autosomal dominant disorder of craniofacial development which has an incidence of approximately one in 50 000 live births.^{4,5} The disorder is characterised by (1) abnormalities of the pinnae (fig 1) which are frequently associated with atresia of the external auditory canals and anomalies of the middle ear ossicles. As a result bilateral conductive hearing loss is common.⁶ (2) Hypoplasia of the facial bones, particularly

the mandible and zygomatic complex (fig 1). (3) Antimongoloid slanting of the palpebral fissures with colobomata of the lower eyelids and a paucity of lid lashes medial to the defect (fig 2). (4) Cleft palate.^{4,5} These clinical features are usually bilaterally symmetrical⁷ (fig 2). While non-penetrance is rare,⁸ diagnosis and subsequent genetic counselling may be very difficult as expression of the gene is extremely variable. Indeed, some patients are so mildly affected that it is difficult to reach a diagnosis. It is therefore important to be able to recognise the minimal diagnostic criteria for the disorder.^{8,9} While 40% of cases have a previous family history, the remaining 60% appear to arise as a result of a de novo mutation. This can create an additional complication in providing genetic counselling where the diagnosis in either of an affected child's parents is in doubt. Conversely, in cases where apparently unaffected parents have produced an affected child, it is very important to be sure that neither parent is, in fact, minimally affected. In this regard the use of craniofacial radiographs, particularly the occipitomeatal view, which enables visualisation of the zygomatic complex, may on occasion prove to be useful.⁹

Differential diagnosis

In the differential diagnosis one should consider the acrofacial dysostoses, where limb abnormalities occur in a patient whose facial gestalt resembles that of Treacher Collins syndrome (Treacher Collins syndrome itself is not associated with anomalies of the limbs). In Nager



Figure 1 Typical features of Treacher Collins syndrome with anomalies of the pinnae and hypoplasia of the zygomatic complex and mandible.

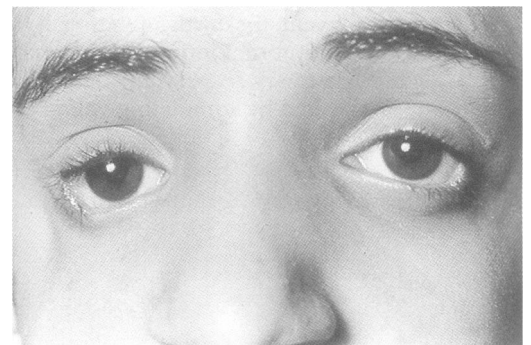


Figure 2 The same child as in fig 1 displaying downward-slanting palpebral fissures with colobomata of the lower eyelids and a paucity of eyelid lashes medial to the defect. Note the bilateral symmetry of the clinical features.

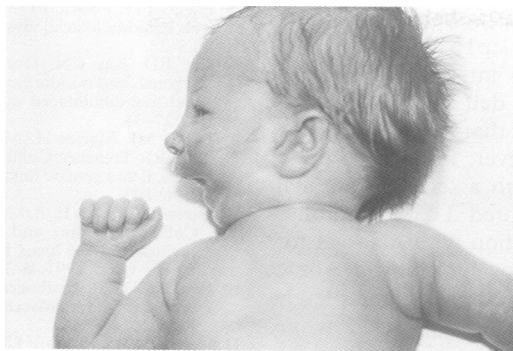


Figure 3 A child with Nager syndrome displaying a facial gestalt similar to that of Treacher Collins syndrome, but with hypoplasia of the thumb.

syndrome the limb defects are preaxial, while in Miller syndrome they are postaxial. The facial features of Nager syndrome are similar to those of Treacher Collins syndrome with zygomatic hypoplasia leading to downward slanting palpebral fissures, micrognathia, anomalies of the external ears, and cleft palate (fig 3). The limb defects, which are often asymmetrical, most commonly include hypoplastic or absent thumbs (fig 3), radial hypoplasia or aplasia, and radioulnar synostosis. In Miller syndrome, as in Nager syndrome, there is some similarity in the facial features to Treacher Collins syndrome, although the limb defects are postaxial, most commonly with absence or incomplete development of the fifth digital ray of all four limbs. While most cases of Nager and Miller syndromes are sporadic, both autosomal dominant and autosomal recessive transmission have been reported.

The oculocardiovertebral (OAV) spectrum should also be considered in the differential diagnosis. This is a complex and heterogeneous set of conditions which includes hemifacial microsomia, which primarily affects development of the ear, mouth, and mandible (fig 4). This condition varies from mild to severe and usually affects only one side of the face (fig 4). Bilateral involvement has occasionally been documented, but in such cases expression is usually more severe on one side of the face.⁷ Goldenhar syndrome, which has vertebral anomalies and epibulbar dermoids in addition to the facial involvement, is also considered part of the OAV spectrum. In most instances, OAV



Figure 4 A girl with hemifacial microsomia in which the pinna and the mandible are affected unilaterally.

spectrum occurs sporadically, although 1 to 2% of cases have a previous family history. Overall, the spectrum is characterised by a low (empirical) recurrence risk, although counselling should be provided on an individual family basis. While it is usually straightforward to exclude OAV from the differential diagnosis of Treacher Collins syndrome on the basis of the facial gestalt, caution should be exercised where patients are only mildly affected so that the minimal diagnostic criteria that constitute Treacher Collins syndrome are not overlooked.

Aetiology and genetics

On the basis that the tissues affected in TCOF1 arise during early embryonic development from the first and second branchial arches, clefts, and pouches, it has been proposed that the condition may arise from abnormal neural crest cell migration or anomalies in the extracellular matrix.^{10,11} Sulik *et al*^{12,13} have produced phenocopies of Treacher Collins syndrome and Nager or Miller syndrome in mice via acute maternal exposure to 13-*cis*-retinoic acid (a vitamin A analogue) at 9.0 to 9.5 days postfertilisation. These studies showed that the craniofacial and limb anomalies resulted from excessive cell death in the proximal aspect of the maxillary and mandibular processes of the first branchial arch and the apical ectodermal ridge of the limb bud. Theories advanced to explain the possible teratogenic mechanisms of vitamin A include its effects on neural crest cell migration and DNA synthesis.¹⁴⁻¹⁶ However, the nature of the genetic defect underlying TCOF1 is unknown.

The gene mutated in TCOF1 was initially mapped at 5q31-34.^{17,18} Owing to the low informativity of the majority of restriction fragment length polymorphisms and the relative shortage of large families, subsequent linkage studies have concentrated on the use of highly informative short tandem repeat polymorphisms (STRPs). These studies have permitted the refinement of the localisation of TCOF1 to 5q32-33.1 and the establishment of markers closely flanking the disease locus.^{19,20} The creation of a combined genetic linkage and radiation hybrid map around TCOF1 has permitted a yeast artificial chromosome contig to be created across the TCOF1 critical region.²¹ Additional STRPs isolated from these YACs, and cosmids derived from them, have permitted the critical region to be reduced to less than 540 kb.

The high density of STRPs surrounding the TCOF1 locus has permitted postnatal diagnostic predictions to be made.⁸ Ideally, diagnostic predictions of this type should only be undertaken in families showing significant evidence of linkage to markers in this region of the genome or when the possibility of heterogeneity has been further minimised by the study of additional families. However, as the majority of TCOF1 pedigrees are relatively small it would be difficult to detect genetic heterogeneity, should this be a feature of the disorder. In this regard TCOF1 has been associated with a number of different chromosomal

anomalies: two apparently balanced translocations, $t(6;16)(p21.31;p13.11)^9$ and $t(5;13)(q11;p11),^{22}$ and two interstitial deletions $del(4)(p15.32p14)^{23}$ and $del(3)(p23p24.12),^{24}$ which raise the possibility that the disorder may be heterogeneous. However, in each of these cases linkage analysis with a series of familial cases from well documented TCOF1 families failed to show cosegregation with markers for the relevant region. Moreover, the chromosome 6 translocation did not ultimately completely cosegregate with the disease phenotype,⁹ while in the remaining cases the facial gestalt of the patients did not entirely conform to the clinical criteria of TCOF1. Furthermore, while genetic heterogeneity in TCOF1 can not be excluded, all of the families that have been analysed to date support linkage of the disease locus to the same region of the genome,^{17-19 25-27} with none showing unequivocal evidence of non-linkage.

To date prenatal diagnosis has only been performed in families with a history of TCOF1 using either fetoscopy²⁸ or ultrasound imaging.^{29 30} While the quality of ultrasound imaging has improved markedly in recent years, allowing non-invasive prenatal diagnosis to be made, it can still be difficult to make a positive diagnosis where the fetus is mildly affected. Prenatal diagnosis using either of these methods can only be performed in the second trimester of pregnancy (approximately 18 weeks) when termination of pregnancy is a particularly traumatic procedure. First trimester prenatal diagnosis would be preferable, particularly if the family feel that termination of pregnancy is desirable in the event that the fetus is affected. The high density of STRPs isolated from the TCOF1 region make this procedure a realistic possibility.

I should like to thank all the Treacher Collins families for their cooperation. I should also like to thank collaborators in the laboratories of Drs John Wasmuth, Katherine Klinger, Greg Landes, and Rakesh Anand, members of my own laboratory (Jill Dixon, Sara Edwards, Amanda Gladwin, and Rahat Perveen), and clinicians who provided patient samples. The financial support of the Wellcome Trust (grant number 036797/Z/92/Z), the Medical Research Council (G9010336CB and G9204430), the Hearing Research Trust, and the Independent Order of Odd Fellows is gratefully acknowledged.

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